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A Century of Crystallography

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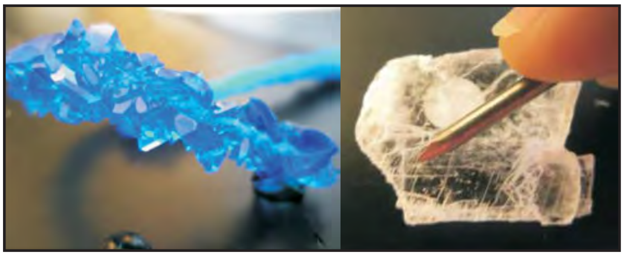
Abstract

The United Nations declared 2014 as the 'International Year of Crystallography' to commemorate 100 years since the award of Nobel Prize in Physics for the discovery of X-ray diffraction by crystals. The International Year of Crystallography 2014 highlights the continuing importance of crystallography and its role in addressing post-2015 development issues such as food security, safe drinking water, health care, sustainable energy and environmental mitigation. The present paper brings out some important applications of crystallography in our life and its future impact.

Throughout history, people have been fascinated by the beauty and mystery of crystals. They are everywhere in nature- in gemstones, glittering snowflakes or grains of salt. The study of crystals' inner structure and properties gave us deepest insights into the arrangement of atoms in the solid state and led to advancements the sciences of solid-state physics, chemistry, biology, medicine and even mathematics, by considering the symmetries behind crystalline and quasicrystalline patterns. Today this field has advanced and the technique has found applications to produce materials with predesigned and controlled properties, from a chemical catalytic agent of industrial interest to toothpaste, vitro-ceramic glass plates, very hard materials for surgical use, or certain aircraft components. The structure of ribosome helps to understand how antibiotics work and therefore we are able to modify their structure to improve efficiency.



Copper(II) Sulfate Rochelle Salt

A crystal is a solid substance made of atoms, molecules or ions that form regular repeating patterns called a crystal lattice. The atoms or ions in crystals are held together by attractive forces often referred to as bonds.

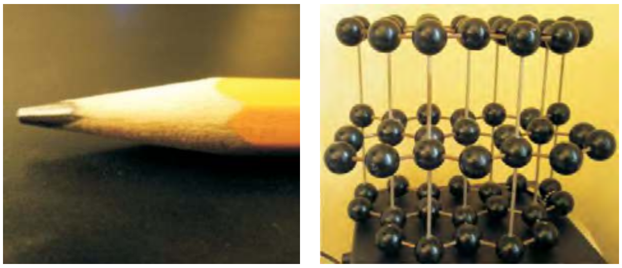
The hardness of a crystal results from the strength of the bonds. When mineralogists study rocks and minerals, they often test for the hardness of these materials. Scientists also study optical properties of crystals. An optical property involves the way a crystal interacts with light. Four common optical interactions with light are color, interference, birefringence, and fluorescence. Crystals often have a characteristic color due to absorption of light, for example hydrated copper(II) sulfate crystals are a characteristic royal blue color. Color may also be caused by interference.

Birefringence

Crystal of Bismuth

Interference often produces rainbows due to the differences in the time that it takes for different colors of light to pass through a material. Bismuth's rainbow colors are due to the varying thickness of an oxide coating. Also referred to as double refraction, birefringence is the splitting of light inside a crystal, causing double vision when looking through the crystal.

Table salt, which has the chemical name of sodium chloride, is a white crystal with a cubic shape. It is made of sodium (Na^+) and chloride (Cl^-) ions. Sugar, ice and diamonds are all crystals. Each has their own shape. Other crystals can be formed from powders that you may have around the house. For example, the detergent booster, borax, contains sodium borate which makes crystals easily. Crystals form as a result of bonds (attractions) between atoms, ions and/or molecules. The particles align themselves to maximize the number of attractions. For example, the Cl– and Na+ ions in sodium chloride attract each other. The unit cell is the smallest repeating portion of the crystal. The unit cell is like a brick and the entire crystal is like a brick wall.

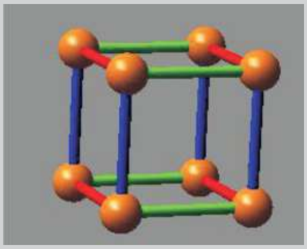


Graphite

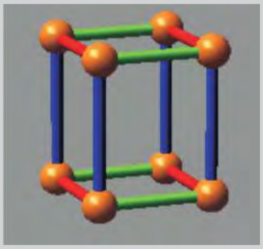
Diamond and graphite (pencil "lead") are forms of carbon. They are very different. Diamond is colorless and very hard. Graphite is black and very soft. These differences come from the different arrangement of atoms in diamond and graphite. It is now well established that a diamond lattice consists of two interpenetrating face centered cubic lattices which are displaced with respect to each other by 1/4th of the lattice spacing in each direction. A face centered unit cubic cell contains four atoms, one at the corner (actually eight corners but each shared by eight cubes) and three at face centers (actually six at the centres of six faces of a cube but each shared by two faces of adjoining cubes). Their fractional positions in the unit are:0,0,0; ½,½,0; ½,0, ½;0, ½,½; Therefore, the diamond lattice contains 8 atoms in the unit cell.

Diamond

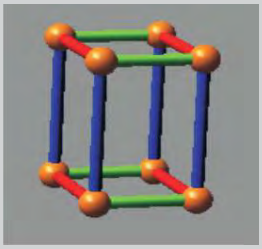
Crystals form in seven different shapes called crystal systems. The crystal systems are named cubic, tetragonal, orthorhombic, monoclinic, triclinic, hexagonal, and rhombohedral. Each crystal system has a unique shape (symmetry). For example all edges (red, green, and blue) in a cubic crystal have the same length. But in a tetragonal crystal one of these lengths (blue) is different than the other two. And in orthorhombic crystals all three are different from one another.



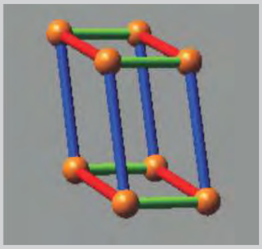
Cubic



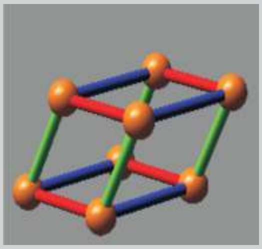
Tetragonal



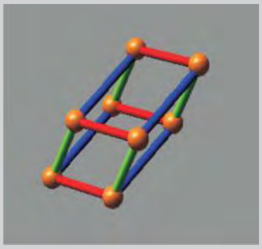
Orthorhombic



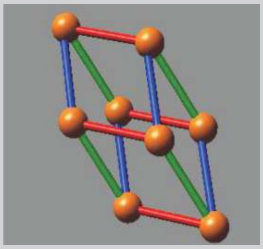
Monoclinic



Hexagonal



Triclinic



Rhombohedral

The history of crystallography began with the work of Johannes Kepler in the 17th century who, in 1611, wrote perhaps the first treatise on geometrical crystallography, with the delightful title, 'A New Year's Gift or the Six-Cornered Snowflake' (Strena Seu de Nive Sexangula). In this he speculates on the question as to why snowflakes always have six corners, never five or seven. He suggests that snowflakes are composed of tiny spheres or globules of ice and shows, in consequence, how the close-packing of these spheres gives rise to a six-sided figure. Kepler was not able to solve the problem as to why the six corners extend and branch to give many patterns (a problem not fully resolved to this day), nor did he extend his ideas to other crystals. Less than 200 years later, French mineralogist René Just Haüy discovered the geometrical law of crystallization.

But perhaps the most crucial leap in understanding came with the work of the father-and-son team the Braggs in 1912. They pioneered a method for uncovering how the atoms in a crystal were arranged. The development of crystallography goes hand in hand with the discovery of X-rays by Wilhelm Röntgen, who in 1895 noted that a high-voltage vacuum tube emitted an unknown type of radiation, which passed through objects to leave an image on a photographic plate.

In 1912, Max Laue established that these penetrating X-rays were like visible light, but with wavelengths thousands of times shorter (about 10-8cm). He surmised that these wavelengths would match the regular spacings between atoms in a simple salt crystal such as copper sulphate. X-rays passing through the crystalline array would thus be diffracted.

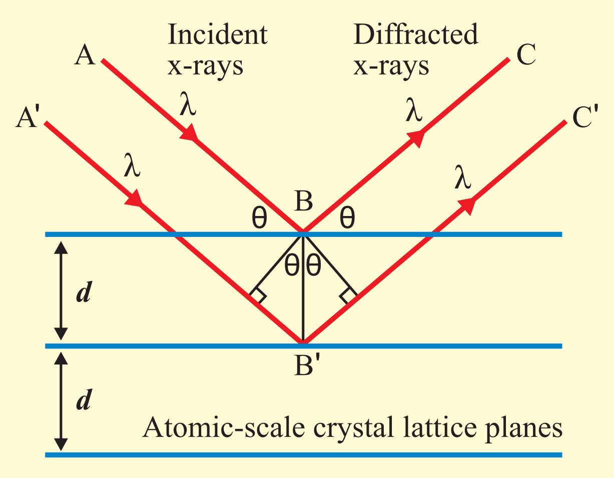
MAX VON LAUE • NOBELPREIS PHYSIK 1914
Röntgenstrahl-Beugung am Kristallgitter
60
DEUTSCHE BUNDESPOST

Max Laue

How exactly does the diffraction pattern obtained relate to the crystal structure? That was explained by William Lawrence Bragg while at the University of Cambridge using a beautifully simple equation known as Bragg's Law – which is now the basis of all modern crystallography.

Bragg's Law

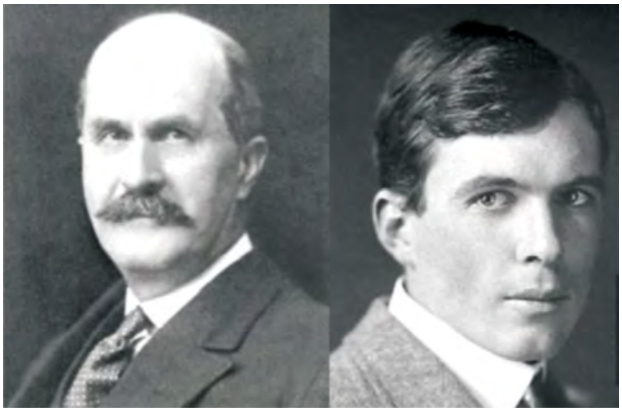
When a crystal is bombarded with X-rays of a fixed wavelength (similar to spacing of the atomic-scale crystal lattice planes) and at certain incident angles, intense reflected X-rays are produced when the wavelengths of the scattered X-rays interfere constructively. In order for the waves to interfere constructively, the differences in the travel path must be equal to integer multiples of the wavelength. When this constructive interference occurs, a diffracted beam of X-rays will leave the crystal at an angle equal to that of the incident beam. When the travel path length difference between the ray paths ABC and A'B'C' is an integer multiple of the wavelength, constructive interference will occur for a combination of that specific wavelength, crystal lattice planar spacing and angle of incidence (Θ). Each rational plane of atoms in a crystal will undergo refraction at a single, unique angle (for X-rays of a fixed wavelength).



The general relationship between the wavelength of the incident X-rays, angle of incidence and spacing between the crystal lattice planes of atoms is known as Bragg's Law and is expressed as :

$$n\lambda = 2d\sin\Theta$$

where n (an integer) is the "order" of reflection, λ is the wavelength of the incident X-rays, d is the interplanar spacing of the crystal and Θ is the angle of incidence.



William Henry Bragg *William Lawrence Bragg*

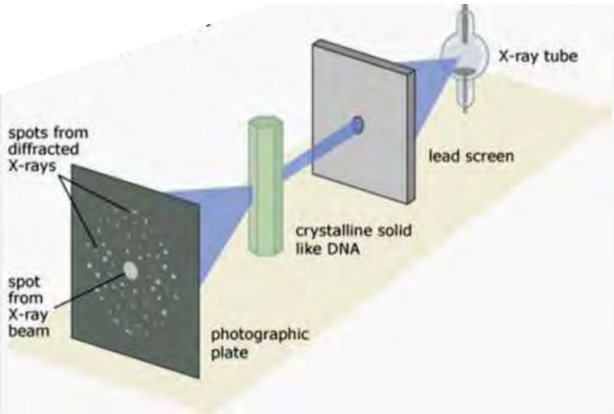
(1890-1971)
Swedish postage stamp with Braggs

William Lawrence Bragg was only 25 when he won the 1915 Nobel Prize in physics, and remains the youngest person ever to win the Nobel Prize. Considered the father of X-ray crystallography, he was the first (together with his father) to use X-rays to determine the arrangement of atoms in simple crystals. In the following years until his retirement in 1965, he was involved with almost all the major developments in X-ray crystallography. From his early solution of scores of inorganic crystals, through his study of metallic alloys, to the solution of complex biological macromolecules such as hemoglobin and DNA, Bragg's life story is also a personal history of the first 50 years of X-ray crystallography and the birth of modern materials science and molecular biology.

Bragg is described as a shy intellectual, a genius who used his understanding of optical diffraction to lay the foundations of X-ray crystallography one simple idea at a time. He was quick to realize that 'Bragg peaks', as we call them today, are formed by the interference of waves diffracted by planes of atoms in the crystal according to 'Bragg's law'. He was first to realize that the peak intensities, not only their positions, hold the information for unlocking the crystal structure, and recognized the importance of overcoming the 'phase problem', which he tackled using ingenious methods.

An important lesson can be learned from Bragg's attitude to research. He approached the problem of crystal structure like solving a puzzle, and believed that all the information required was contained within the diffraction pattern. He didn't care to learn the detailed chemistry or biological function of the molecules, nor did he study quantum mechanics as did all his contemporaries. It seems that Bragg didn't believe in fancy theory but rather in simple logic, grounded in his fundamental grasp of physics. Bragg invented experimental devices for doing some of his theory.

X-ray diffraction, developed in the first half of the 20th century, was one of the new technologies that made solving the structure of DNA possible. The technique works on crystals, a kind of molecule with a regular, repeating structure. When X-rays are aimed through a sample, they are bent or diffracted in different directions depending on the locations of the atoms in the sample, and the final direction of the X-rays can be



X-ray Diffraction Technique

recorded on film. Because the X-rays must travel through many layers of atoms, it's important that the atoms always occur in the same crystalline arrangement. If they don't, the X-rays are bent into overlapping patterns, leaving the results a fuzzy, indistinct blur. However, if the structure has a repeating arrangement of atoms, they leave a pattern of sharp, clear spots. Different structures scatter the X-rays into different characteristic patterns.

Even though scientists couldn't directly observe the atoms within the crystal, they could work backward from X-ray diffraction patterns to reconstruct the three-dimensional structure that produced the scattering. This works a little like trying to figure out how tall a person is by looking at his or her shadow. Depending on the angle of the sun, the shadow might be longer or shorter, but if we could compare many pictures of their shadow at different times of day, we would eventually be able to figure out how tall they were. Similarly, scientists compare many "shadows," or X-ray diffraction patterns, cast by a crystal to determine the arrangement of atoms within it.

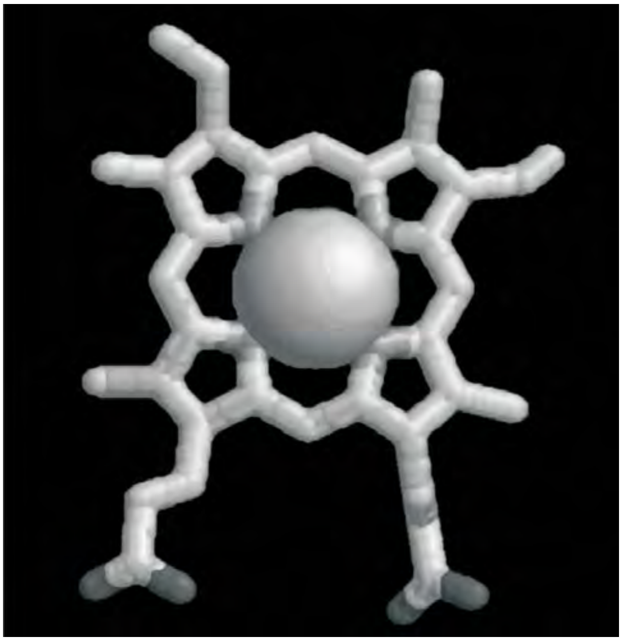
An essential step in X-ray crystallography is growing high-quality crystals. The best crystals are pure, perfectly symmetrical, three-dimensional repeating arrays of precisely packed molecules. They can be different shapes, from perfect cubes to long needles. Most crystals used for these studies are barely visible (less than 1 millimeter on a side). But the larger the crystal, the more accurate the data and the more easily scientists can solve the structure. Crystallographers grow their tiny crystals in plastic dishes. They usually start with a highly concentrated solution containing the molecule. They then mix this solution with a variety of specially prepared liquids to form tiny droplets (1-10 microliters). Each droplet is kept in a separate plastic dish or well. As the liquid evaporates, the molecules in the solution become progressively more concentrated. During this process, the molecules arrange into a precise, three-dimensional pattern and eventually into a crystal. Sometimes, crystals require months or even years to grow. The conditions - temperature, pH (acidity or alkalinity), and concentration - must be perfect. And each type of molecule is different, requiring scientists to tease out new crystallization conditions for every new sample. Even then, some molecules just won't cooperate. They may have floppy sections that wriggle around too much to be arranged neatly into a crystal. Or, particularly in the case of proteins that are normally embedded in oily cell membranes, the molecule may fail to completely dissolve in the solution.

Copper Sulfate - $CuSO_4$ - One of the first crystals to be examined by x-ray diffraction.

Crystallography, can be broken down into two main areas - the study of small molecules and the study of large molecules. X-ray crystallography is the fundamental research tool that shaped our notion on biological structure & function at the molecular level. It generates the information vital to understand life processes by providing the information required for creating accurate three-dimensional models. The power of this method inspired continuous efforts and spectacular innovations, which vastly accelerated its incredible expansion. Consequently, over the last six decades biological crystallography has produced a constantly growing number of structures, some of which were considered formidable. This remarkable advance yielded numerous new insights into intricate functional aspects.

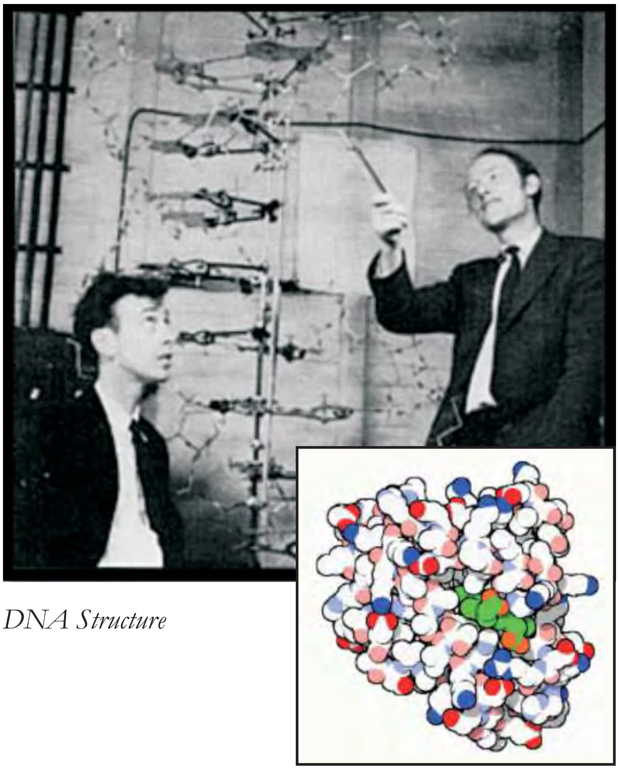
Proteins, macromolecules involved in everyday functions of the body such as transporting oxygen and chemicals in blood, forming major components of muscle and skin, and fighting disease, come in over 100,000 varieties. Active sites on molecules of proteins, when inappropriately triggered or absent, can cause disease or an unwanted function. Scientists seek to locate those active sites so drug designers can understand their function and then, in some cases, work to block them or render them inactive. For example, the anti-inflammatory drug ibuprofen works on a specific protein, which is involved early in the signaling process that tells your body that inflammation should occur. Blocking the active site on this protein prevents or reduces the inflammation.

The first known published observation of the crystallization of a protein was made by F.L. Hunefeld in 1840 at Leipzig University in Germany. While working with hemoglobin, Hunefeld obtained flat, plate-like crystals of this protein when he pressed the blood of an earthworm between two slides of glass and allowed the blood to dry very slowly. In 1851, Otto Funke, another German researcher, published a series of articles in which he described growing hemoglobin crystals by successively diluting red blood cells with a solvent such as pure water, alcohol or ether, followed by slow evaporation of the solvent from the resulting protein solution.



Molecular structure of the heme ring in the hemoglobin molecule

Early on, scientists grew crystals solely to purify proteins. Not until the 1930's did researchers begin to focus their attention on crystals as a source of structural information about protein molecules. They turned to X-ray diffraction, a procedure in which a pencil-lead-sized X-ray beam is directed at a crystal. The X-ray beam is scattered by the crystal, producing a signal that results in tiny pinpoints that can be recorded on film. Data from this recorded X-ray diffraction pattern has a direct relationship to the protein's molecular structure and can be used to help reveal the structure of a molecule of the particular protein under investigation. By the 1960's, scientists were investigating the molecular structures of an abundance of crystals grown by biochemists.



DNA Structure

Myoglobin Structure

The full flowering of biological crystallography began in the 1960s, heralded by the 1964 Nobel Prizes in Medicine and Chemistry. The awards to Crick, Watson and Wilkins for the structure of DNA and to Kendrew and Perutz for the first protein structures (myoglobin and haemoglobin) both depended on X-ray diffraction.

Myoglobin was the first protein visualized in three dimensions at the atomic level by X-ray crystallography, laying the foundation for a new era of biological understanding. For this discovery, John Kendrew and Max Perutz shared the 1962 Nobel Prize in Chemistry. In 1959 Max Perutz, whose methodological work had been crucial to Kendrew's success, determined the structure of hemoglobin, a protein closely related to myoglobin and the second to be analyzed by X-ray crystallography. It can be said fairly that without crystallography the molecular biology of today could not exist.

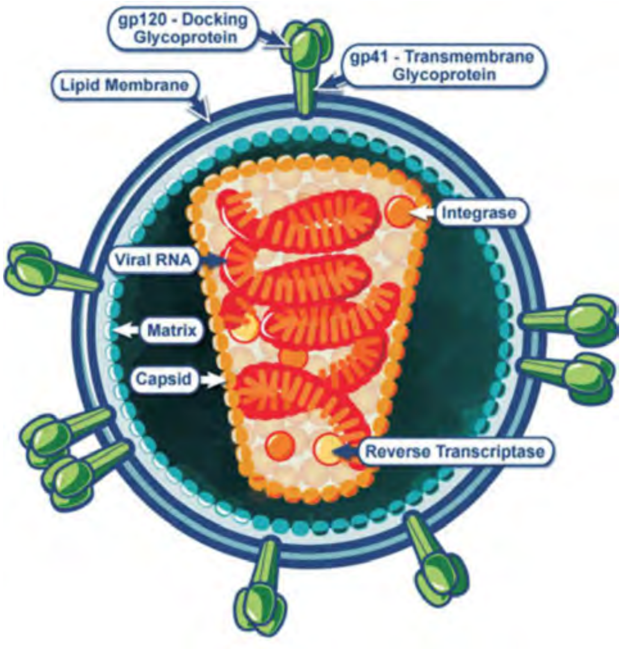
A living cell is extremely crowded, with thousands of different proteins and other molecules jostling for space (the total protein concentration is estimated at about 30 g/L). In this environment, specificity is everything; a protein must perform its own task, efficiently and without error, and the 3D structure of a protein is critical, defining its chemistry and the spatial constraints on its substrates. Secondly, structural knowledge provides new opportunities for applications, in areas such as structure-based drug design, or in the development of new tools in biotechnology.

Historically, the discovery of drugs has largely been a process of trial-and-error. The targets of these medicines were unknown and side effects were discovered the hard way. As more has been learned about the molecular basis of disease, it has become possible to develop drugs specifically against deliberately-chosen targets. Crystallography, and knowledge of protein 3D structure, is now playing an ever-increasing role in this approach to new medicines, as is illustrated by drugs developed against two viral diseases, HIV-AIDS and Influenza.

The near-panic that came with the AIDS epidemic of the 1980s led to the first triumph for crystallography and structure-based drug design. The goal in this approach is to find a protein that is critical to the survival or spread of the infectious agent, solve its structure and design specific inhibitors against it. In the fight against AIDS, two key targets, the HIV protease and the HIV reverse transcriptase, were quickly crystallized and their structures solved. The HIV protease proved to be druggable and within seven years the first drugs were in the clinic. Although not a cure, the drugs continue to be improved, and the disease is now manageable. The beauty of the structure-based approach is that knowledge of exactly how a molecule binds to its target enables a medicinal chemist to see exactly where a substituent might be added, or where it cannot be, during the difficult process of optimization.

In 1999, researchers determined the crystal structure of a complete ribosome for the first time. The work was a technical triumph for crystallography. Even today, the ribosome remains the largest complex structure obtained by crystallography.

Ribosomes make the stuff of life. They are the protein factories in every living creature, and they churn out all proteins ranging from bacterial toxins to human digestive enzymes. To most people, ribosomes are extremely small —tens of thousands of ribosomes would fit on the sharpened tip of a pencil. But to a



Structure of HIV

Examining ribosomal structures in detail will help researchers better understand the fundamental process of protein production. It may also aid efforts to design new antibiotic drugs or optimize existing ones.

structural biologist, ribosomes are huge. They contain three or four strands of RNA and more than 50 small proteins. These many components work together like moving parts in a complex machine - a machine so large that it has been impossible to study in structural detail until recently. Ribosomes are complex molecular machines that serve as the primary site of biological protein synthesis. They are composed of two independent subunits of unequal size, which associate upon initiation of protein biosynthesis. Due to their enormous size, tendency to deteriorate, and functional heterogeneity, ribosomes are extremely challenging to crystallize. For determining the detailed structure and mechanism of the ribosome Venkatraman Ramakrishnan, Thomas A. Steitz and Ada E. Yonath were jointly awarded the Nobel Prize in Chemistry in 2009.

The complexity of biological systems demands exquisite control of specificity and a crucial role for three-dimensional structure. Structural biology thus provides a natural bridge between chemistry and biology by its ability to define biological systems and mechanisms at an atomic level. Remarkable technological advances in X-ray crystallography over the past 20 years, coupled with developments in NMR and cryo-electron microscopy (not discussed in this article, but highly complementary) now make biological structural information highly accessible. Many of the steps in structure determination are beginning to be automated. The frontier has shifted to the more challenging systems – membrane proteins, protein-protein complexes, biological machines and assemblies – for which the key requirements are to find tractable forms for analysis. Behind these frontier targets, however, the structures of simpler proteins will provide the knowledge that fuels many applications in biomedicine, biotechnology and nano-science. Above all, this is still discovery science, with many more of Lawrence Bragg's gold nuggets yet to be found.

Future Challenges

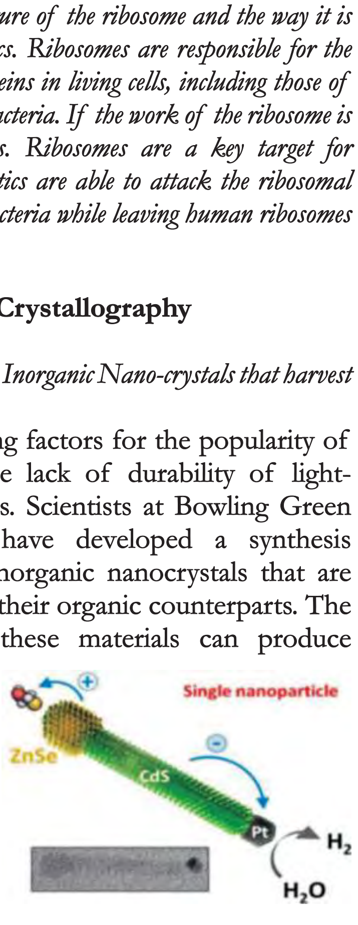
The following are some examples of how crystallography can :

- *help improve water quality in poor communities, for instance, by identifying new materials which can purify water for months at a time, such as nanosponges (tap filters) and nanotablets. It can also help to develop ecological solutions to improve sanitation.*
- *develop new products which lower home's energy consumption (and heating bill) while curtailing carbon emissions, such as insulating materials. It can also identify new materials which reduce the cost of solar panels, windmills and batteries while making them more efficient, to reduce wastage and improve access to green technologies.*
- *contribute to the development of ecological construction materials in developed and developing countries. It can also help to reduce pollution by replacing chemical solvents with 'green' inorganic solvents based on ionic liquids and CO2. It can help to reduce mining waste and related costs by contributing to methods which selectively extract only the materials required.*
- *tackle the growing resistance of bacteria to antibiotics, for instance. Together with Venkatraman Ramakrishnan and Thomas Steitz, crystallographer Ada Yonath has managed to determine the structure of the ribosome and the way it is disrupted by antibiotics. Ribosomes are responsible for the production of all proteins in living cells, including those of humans, plants and bacteria. If the work of the ribosome is impeded, the cell dies. Ribosomes are a key target for antibiotics, as antibiotics are able to attack the ribosomal activity of harmful bacteria while leaving human ribosomes untouched.*

Latest R&D News in Crystallography

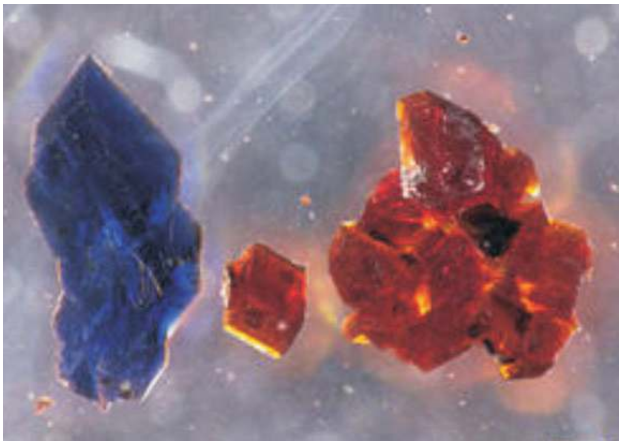
A. *Researchers synthesize Inorganic Nano-crystals that harvest Solar Energy*

One of the limiting factors for the popularity of solar energy is the lack of durability of light-absorbing materials. Scientists at Bowling Green State University have developed a synthesis method for two inorganic nanocrystals that are each tougher than their organic counterparts. The liquid phase of these materials can produce hydrogen gas or an electric charge. The article, published in Journal of Visualized Experiments (JoVE),



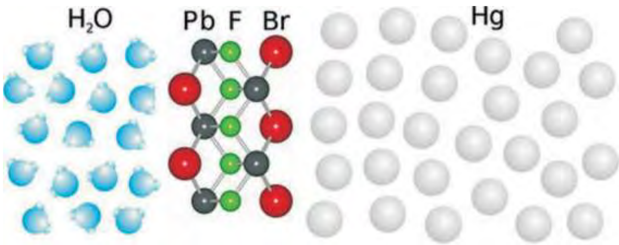
B. *A Crystal of a Different Color*

Chemists have unexpectedly made two differently colored crystals—one orange, the other blue—from one chemical in the same flask while studying a special kind of molecular connection called an agostic bond. The discovery, reported in *Angewandte Chemie International Edition,* is providing new insights into important industrial chemical reactions such as those that occur while making plastics and fuels. One flask of chemicals gives rise to either blue or orange crystals.



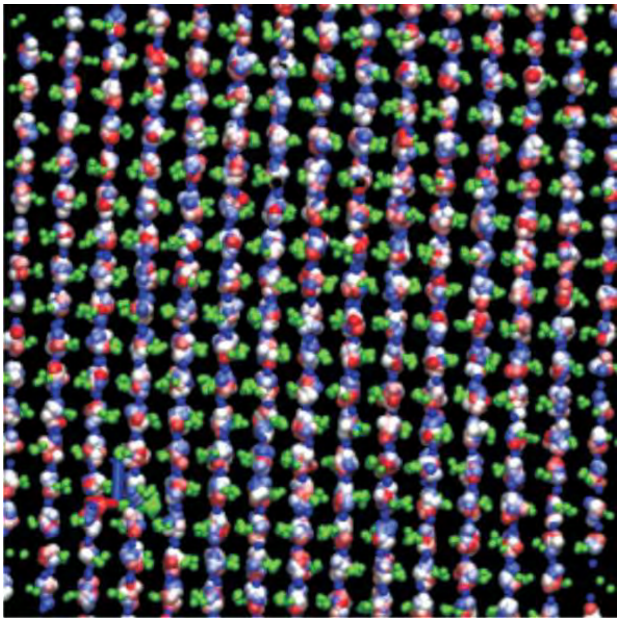
C. *Nano-crystals grow from Liquid Interface*

An international collaboration of scientists has discovered a unique crystallizing behavior at the interface between two immiscible liquids that could aid in sustainable energy development. Liquid interface behavior cannot be investigated at atomic level by most modern methods. Only brilliant X-rays at world-leading light sources can investigate this type of important chemical processes. The result is reported on in the *Proceedings of the National Academy of Science* in an article titled "In situ x-ray studies of adlayer-induced crystal nucleation at the liquid-liquid interface". The image shows the Illustration of the nano-layer at the liquid interface between the salt solution and mercury. Physicists from Kiel University discovered the formation of an ordered crystal of exactly five atomic layers between the two liquids with brilliant X-rays.



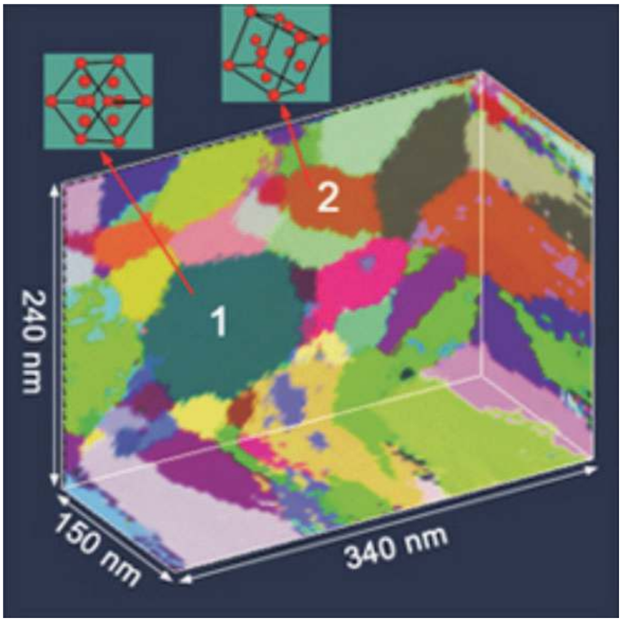
D. *Crystals for Efficient Refrigeration*

Researchers at the Carnegie Institution have discovered a new efficient way to pump heat using crystals. The crystals can pump or extract heat, even on the nanoscale, so they could be used on computer chips to prevent overheating or even meltdown, which is currently a major limit to higher computer speeds. The research is published in the Physical Review Letters. The image shows a molecular dynamics simulation of lithium niobate under a time varying electric field, which changes the sign of the polarization. Red is niobium, green is oxygen, and lithium shows a range of colors for different time steps. The niobium and oxygen are shown only for one time step for clarity.



E. *Looking inside Nano-materials in Three Dimensions*

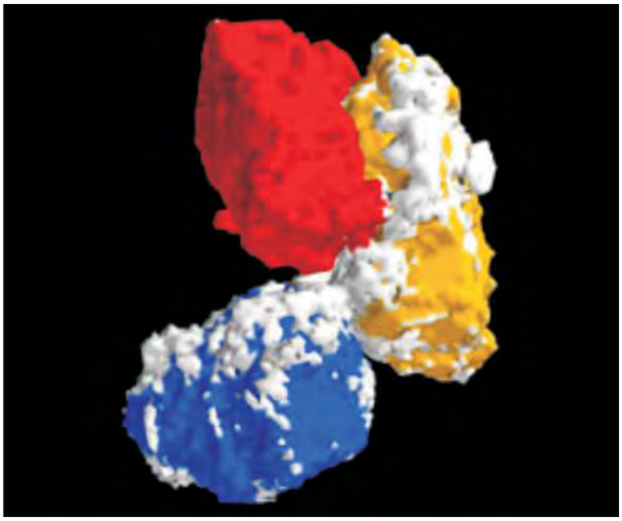
An international team of scientists have developed a new technique using a transmission electron microscope (TEM) that allows 3D mapping of the crystal structure inside a material. Unlike previous methods using x-rays, the TEM can determine structures down to a nanometer in size. An example of such a 3D map is given in the figure, showing the arrangement of crystals in a 150nm thick nano-metal aluminum film. The crystals have identical lattice structure (arrangement of atoms)



but they are orientated in different ways in the 3D sample as illustrated by the labels 1 and 2. The colours represent the orientations of the crystals and each crystal is defined by volumes of the same colour. The individual crystals of various sizes (from a few nm to about 100 nm) and shapes (from elongated to spherical) are clearly seen and mapped with a resolution of 1 nanometer.

F. *X-rays Create a Window on Glass Formation*

Scientists have for the first time visualized the transformation of powder mixtures into molten glass. A better understanding of this process will make it possible to produce high quality glass at lower temperatures, leading to significant energy savings in industrial glass manufacturing. The results are published in the Journal of the American Ceramic Society. The image showing the reaction between a grain of sodium carbonate (red) and two grains of silica (blue and yellow). These reactions produced sodium silicates, the precursors of glass. The grain of sand measures about 100 nm across.



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